TRANSPLANTATION OF AN UNPAIRED ORGAN, THE HEART

NORMAN E. SHUMWAY

DIVISION OF CARDIOVASCULAR SURGERY, STANFORD UNIVERSITY SCHOOL OF MEDICINE

The advent of clinical cardiac transplantation has been accompanied by a public fanfare unprecedented in medicine. This unfortunate situation has tended to obscure the long history of experimental heart transplantation and the relationship of clinical heart transplantation to previous work in renal and hepatic homotransplantation. This discussion is a review of past experimental work with a note on current clinical results at Stanford University Hospital.

A decade ago three principal obstacles to orthotopic homotransplantation of the heart were easily identified in the laboratory: (1) difficulties in the development of a satisfactory surgical technique; (2) demonstration of adequate post-transplantation function of the heart in the absence of central nervous system influence; and (3) method for control of the homograft rejection phenomenon. No consideration of human application would be acceptable without the prior resolution of these three problems in the laboratory.

Surgical Technique.—In 1959 the concept of atrial-to-atrial anastomosis for cardiac transplantation rather than multiple venous anastomoses was developed and successfully applied. Preservation of the heart during the obligatory period of anoxia was accomplished by simple immersion in cold saline to reduce the metabolic requirement. Safe ischemic time ranged up to six hours in the experimental laboratory, and routine survival of the host animal was achieved. Cardiopulmonary bypass was used to support the recipient.

Performance Characteristics of the Heart Transplant.—Immediately after cardiac transplantation a diminution in cardiac output was noted for 24 to 48 hours. After the third day, values for cardiac output increased to the normal range. Ablation of normal regulatory mechanisms was reflected by an absence of respiratory sinus arrhythmia, an increased plasma volume, a decreased diuretic response to saline loading, and absence of the Bainbridge reflex. In the exact physiological replica of the homograft minus the immune reaction, the cardiac autograft, definite evidence of both vagal and sympathetic reinnervation could be detected one year postoperatively. Physiological impairment secondary to heart transplantation appeared to be temporary and minimal, and one could speculate that if the subject survived long enough, cardiac reinnervation might occur even across the homograft barrier.

Control of the Homograft Rejection Phenomena.—The orthotopic homotransplanted heart was then studied histologically and electrocardiographically in the experimental laboratory to correlate changes in the cardiogram with pathologic lesions. Two kinds of pathologic lesions were simultaneously noted; one was a cellular destruction of myocardium, and the second was a direct attack on the vascular endothelium. Rejection was invariably accompanied by myocardial edema and could be detected through examination of the electrocardiogram. The QRS amplitude regularly diminished starting about four days before death in animals undergoing cardiac rejection. Using the electrocardiogram as an early herald of homograft rejection, we obtained prolonged survival of animals

after orthotopic homotransplantation of the heart. The use of azathioprine and methylprednisolone during periods of suspected homograft rejection crises produced the first long-term survival of any living animal after cardiac replacement.

Clinical Experience.—With this background, initial clinical trials at Stanford were performed in January 1968. To date (5/26/69), 14 patients have undergone cardiac transplantation with six patients presently surviving—9, 7, 6, $3^1/_2$, $1^1/_2$, and $^1/_4$ months post-transplantation. Homograft rejection has been noted in every patient who has survived any considerable period of time, except one. Rejection has been identified by a fall in QRS amplitude, the presence of atrial arrhythmias, a rightward shift in the frontal plane axis, an increase in cardiac diameter and posterior wall thickness as revealed by ultrasound cardiography, and the appearance of an early diastolic gallop rhythm. Rejection has been reversed in all but two patients with the appropriate administration of azathioprine, methylprednisolone, actinomycin D, and antilymphocyte globulin. At the present time mortality statistics are comparable with unrelated renal transplants according to the Kidney Transplant Registry, 40 per cent one year survival. In 12 patients who were accepted for transplantation of the heart at Stanford but who for one reason or another were not transplanted, the longest survival was three months, and the mean survival was less than one month. Although leukocyte antigen profiles for tissue typing have been obtained between each set of donor-recipient pairs, we are unable to predict the clinical course from the number of mismatches. Theoretically, and certainly eventually, the importance of tissue typing will be established, but at this point in medical history with respect to cardiac transplantation, information in the general area of tissue typing is being derived in a retrospective manner.

Three criteria have been developed for recipient selection, and when these criteria are scrupulously respected, clinical heart transplantation appears to be justifiable in the light even of present knowledge. The criteria for recipient selection are (1) total incapacity of the patient with a prospect of imminent death; (2) complete clinical evaluation with cardiac catheterization and cineangiocardiography denoting the precise cardiac lesion; and (3) agreement that intensified medical management or a lesser surgical procedure has nothing to offer the patient. Clearly, an irreducible operative mortality will endure utilizing these criteria for heart transplantation, and in several instances patients were in the process of dying at the time cardiopulmonary bypass was instituted for resuscitation and transplantation of the recipient.

Conclusions.—Heart transplantation is therapeutic from the perspective of the designated recipient. Heart transplantation continues, however, to be a field of clinical investigation from the viewpoint of the medical scientists involved. Concomitant with any clinical program in heart transplantation, intense laboratory work should continue in an effort to evaluate such controversial issues as the importance of tissue typing, the problem of prior sensitization from previous transplantation, heart transplantation in the very young, and protocols of improved immune suppression. Finally, the suspected accommodation or adaptation which appears to develop with time between host and donor heart requires documentation and elucidation.